UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/540,539 | 10/04/2006 | Rouli Zhou | 062331-5002 | 8365 |

9629 7590 06/09/2008

MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

| EXAMINER | |
|---|---|
| GUSSOW, ANNE | |
| ART UNIT | PAPER NUMBER |
| 1643 | |
| MAIL DATE | DELIVERY MODE |
| 06/09/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/540,539 | ZHOU ET AL. | |
| | Examiner | Art Unit | |
| | ANNE M. GUSSOW | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-14 and 16-21* is/are pending in the application.

4a) Of the above claim(s) *7-11,14 and 17-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,12,13 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 1-6, 12, 13, and 16 have been amended.

Claim 15 has been cancelled.

2. Claims 1-6, 12, 13, and 16 are under examination.

3. The following office action contains NEW GROUNDS of Rejection.

### *Priority*

4. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. The translation of the Chinese priority document has been received. The instant claims receive priority to the Chinese document. For art rejection purposes, the claims receive the priority date of December 24, 2002.

### *Objections Withdrawn*

5. The objections to the specification are withdrawn in view of applicant's amendments to the specification.

***Rejections Withdrawn***

6. The rejection of claims 1-6, 12, 13, 15, and 16 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of applicant's amendment to the claims.

7. The rejection of claims 1-6, 12, and 13 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of applicant's amendment to the claims.

8. The rejection of claims 1-6, 12, 13, 15, and 16 under 35 U.S.C. 112, first paragraph, as lacking enablement is withdrawn in view of applicant's amendment to the claims.

9. The rejection of claims 1-6, 12, 13, 15, and 16 under 35 U.S.C. 101 as being directed to non-statutory subject matter is withdrawn in view of applicant's amendment to the claims.

10. The rejection of claims 1, 2, and 6 under 35 U.S.C. 102(b) as being anticipated by Shao, et al is withdrawn in view of applicant's perfection of the foreign priority claim.

11. The rejection of claims 1 and 5 under 35 U.S.C. 102(b) as being anticipated by Shao and Zhou is withdrawn in view of applicant's perfection of the foreign priority claim.

12. The rejection of claims 1, 6, 12, and 13 under 35 U.S.C. 102(b) as being anticipated by Kato, et al. is withdrawn in view of applicant's amendment to the claims.

13. The rejection of claims 15 and 16 under 35 U.S.C. 102(b) as being anticipated by Shao, et al. is withdrawn in view of applicant's perfection of the foreign priority claim and amendment to the claims.

## *NEW GROUNDS of Rejection*

### *Claim Rejections - 35 USC §§ 101 and 112, First Paragraph*

14. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 1-6, 12, 13, and 16 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

The claims are directed to a cancer-related polynucleotide sequence of SEQ ID Nos. 1-3, or 6 and a polynucleotide sequence that encodes the polypeptide of SEQ ID No. 4 or SEQ ID No. 7. The utility and enablement of the polynucleotide depends upon

whether or not the polynucleotide or the polypeptide it encodes has utility and enablement.

The specification discloses that SEQ ID No. 1 and SEQ ID No. 6 are related to an increased risk of developing hepatocellular carcinoma. The specification discloses that SEQ ID No. 4 is encoded by the whole sequence of SEQ ID No. 1 (page 3, lines 17-18). The specification discloses that the protein encoded by SEQ ID No. 6 should contain 370 amino acid residues of SEQ ID No. 7 (page 8, lines 24-25, emphasis added) however, there is no direct evidence that the polypeptide of SEQ ID No. 7 is produced. The specification discloses that the allele of SEQ ID No. 6 has been derived by PCR cloning (page 8 lines 14-15). The specification discloses detection of the polypeptide of SEQ ID No. 4 in some epithelium derived cancers (page 4). The specification does not disclose detection of the polynucleotides of SEQ ID Nos. 2-3 or the polypeptide of SEQ ID No. 7 either in normal or cancerous cells. Therefore, the polynucleotides are not cancer-related and the polypeptide is a totally new, uncharacterized polypeptide with no well-established utility.

The data for LAPTM4B genomic DNA have no bearing on the utility of the claimed polypeptide. In order for the LAPTM4B polypeptide to be overexpressed in tumors, amplified genomic DNA would have to correlate with amplified mRNA, which in turn would have to correlate with amplified polypeptide levels. The art discloses that such correlations cannot be presumed. Regarding the correlation between genomic DNA amplification and increased mRNA expression, see Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that:

> "An analysis of *WISP*-1, gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors." See also Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract). Even if increased mRNA levels could be established for LAPTM4B, it does not follow that polypeptide levels would also be amplified. Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). Also, Hu et al (2003, Journal of Proteome Research 2(4):405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no

evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, most are attributable to disease-independent differences between the samples (emphasis added; 2003, Nature Biotechnology 21:976-977).

The art also shows that transcript levels do not correlate with polypeptide levels in normal tissues. See Haynes et al (1998, Electrophoresis 19:1862-1871), who studied more than 80 polypeptides relatively homogeneous in half-life and expression level, and found no strong correlation between polypeptide and transcript level. For some genes, equivalent mRNA levels translated into polypeptide abundances, which varied more than 50-fold. Haynes et al. concluded that the polypeptide levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Gygi et al. (1999, Mol. Cell. Biol. 19:1720-1730) conducted a similar study with over 150 polypeptides. They concluded that

> "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 2-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 3-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA

transcript analysis is insufficient" (see Abstract).

Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract). Additionally, Hanash S (Nature Reviews, Applied Proteomics Collection, pp. 9-14, March 2005) states "For example, a gene can be amplified 100-fold in certain tumors with no demonstrable effect on RNA levels for that gene." "Alternatively, protein levels can be increased, decreased or modified with no demonstrable changes in the levels of their corresponding RNAs." (see page 9). Hanash also indicates "no single type of molecular approach fully elucidates tumor behavior, necessitating analysis at multiple levels encompassing genomics and proteomics" (see abstract). Human tumors are more complex and heterogenous than expected, and are caused by defects in numerous pathways and factors at many levels and incorporation of different genome-scale global profiling are expected to lead to molecular-based classifications of cancer that transcend organ and tissue types and supercede classifications based on the expression patterns of genes with unknown functional significance as in the present case for LAPTM4B.

Therefore, data pertaining to LAPTM4B genomic DNA do not indicate anything significant regarding the claimed LAPTM4B polypeptides. Significant further research

would have been required of the skilled artisan to reasonably confirm that LAPTM4B SEQ ID Nos. 2-3 or 7 are overexpressed in any cancer to the extent that it could be considered cancer-associated, and thus, the asserted utility is not substantial. Thus, the proposed polynucleotides and encoded polypeptide of the claimed invention are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field" and "a patent is not a hunting license" "[i]t is not a reward for the search, but compensation for its successful conclusion."

17. Claims 1-6, 13, 14, and 16 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

## ***Conclusion***

18. No claims are allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNE M. GUSSOW whose telephone number is

(571)272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow

June 2, 2008

/David J Blanchard/
Primary Examiner, Art Unit 1643